Newly Developed Treatments for Acute Lymphoblastic and Acute Myeloid Leukemia

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ABSTRACT: Chemotherapy has been dominating the field of cancer treatment for a long time, however, its limitations have been revealed over time. Therefore, several antigen proteins and chimeric antigen receptor-T cells (CAR-T) involved in the immunotherapy of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) have been introduced. This paper provides details on the mechanisms, implemented investigations, and drawbacks of the immunotherapy for ALL and AML. Current studies have shown that CAR-T cell therapy can eliminate pediatric ALL relapse along with treating B cell ALL. With the appearance of CAR-T cell therapy, especially CD19-, CD20-, and CD22-directed CAR-T cells, aggressive acute lymphomas involving ALL become treatable. Studies have also shown that AML can be treated with FLT3 inhibitors and immunotherapy including monoclonal antibodies (mbA) and CD33-, CD123-directed CAR-T cells. Anti-CD33 monoclonal antibodies can combine with calicheamicin, a cytotoxic agent in DNA strand cleavage, and monotherapy of gemtuzumab ozogamicin (GO), an antibody-drug conjugate, and this combination has been proved to extend the overall survival of both newly treated patients and R/R AML patients who are unable to tolerate standard chemotherapy.

1. INTRODUCTION

Leukemia is seen as a clonal expansion of hematopoietic stem cells in the bone marrow or a kind of production of aberrant leukocytes through a primary or secondary process. Based on the rapidity of proliferation, leukemia is categorised as an acute or chronic, and myeloid or lymphoid disease, depending on the originator cell. Prevailing subordinate types include acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL). Acute lymphoblastic and acute myelogenous are the predominating types. Acute leukemia develops at a rate faster than chronic leukemia as bone marrow cells have occupied around 1-5% of bone marrow and blood smear. Current treatments for leukemia are immunotherapy and chemotherapy. Instead of using a targeted agent alone in immunotherapy, it is implementable to develop other kinds of therapies, for instance, the therapy with selected targeted agents and anti-CD20 monoclonal anti-bodies is a well-used combination [2]. This article aims to provide details on the mechanism of ALL and AML, and introduce current treatments along with their flaws. The latest development of immunotherapy treatment involving CAR-T cells, monoclonal antibodies, and FLT3 inhibitors will be introduced in detail with data from recent clinical trials, thus complementing previous research. As CAR-T cell therapy is an emerging research field, there have not been many details about it, but investigations are carried out each year with various methods, hence more information will be provided in this paper compared to those in previous years.

2. ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

2.1. Mechanism of acute lymphoblastic leukemia

ALL is frequently observed in young people, with a peak incidence in children aged between 2 and 5. Blast transformation of B and T cells is commonly inspected in children with leukemia, which is responsible for 80% of the cases in the paediatric group compared to 20% in adults [2]. Clinical features of T-cell ALL are relatively more complex than B-cell ALL due to the factors such as a high occupation of mediastinal mass and a high leukocyte count at diagnosis. Supported by developed chemotherapy procedures, the complete response (CR) rate and the clearance of all signs of cancer in adults with ALL is 80% to 90% but with a relatively low cure rate of 40% to 50%. Hence, the invention of competent therapies becomes necessary [2].

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2.2. Newly developed treatment for acute lymphoblastic leukemia

2.2.1. Immunotherapy: monoclonal antibodies (mAb)

ALL leukaemia cells express several surface antigens responsive to target therapies, involving CD20, CD22, and CD19. These antibodies aim at these leukaemia surface antigens selectively, and reduce the toxicity brought by missed targets [1]. CD20 is a protein revealed on B cell surface. Around 30–50% of B cell lymphoblasts precursors will present it on their cell surface. mAb is currently used in ALL trails associated with rituximab, ofatumumab, and obinutuzumab [3]. As for CD19, its common directed therapy involves SAR3419, an artificial monoclonal antibody associated with an anti-mitotic agent which fits the same site on tubulin as vincristine [1]. Another therapy that involves CD19 is blinatumomab. In a phase 3 trial, adults were randomly given densely pre-processed B-cell precursor ALL to accept either blinatumomab or normal chemotherapy in a 2:1 ratio. The overall survival period for the group of blinatumomab is greatly longer than the group with normal chemotherapy [4]. CD19 can be rapidly incorporated after binding to an antibody, becoming an ideal participant for the immunoconjugate therapy [5].

CD22 is revealed on the leukemic blasts of over 90% of patients with acute leukemia, and it swiftly binds to antibodies via endocytosis. CD22 is used as a target for antibodies, supported by the clinical success of in vivo applicants of therapeutic antibodies. One of the characteristics of the Siglec family is that the receptor internalization, which happens immediately after the ligation to antibodies, enables CD22 to deliver cytotoxic hits well, calicheamicin in particular [1] [6]. CD22 is the member of Siglec family which can recognize glycan ligands joined with glycoproteins or glycolipids. NeuAc liposomes are created in recent trials in comparison with naked liposomes. Results have shown that NeuAc liposomes are able to interact with CD22 on the cell surface membrane whereas naked liposomes cannot. This is because of the characteristic of receptor internalization. Inotuzumab ozogamicin (InO) therapy is associated with CD22 and targets CD22 by InO in ALL blasts. Fission in DNA double-strand and subsequent apoptosis take place once InO binds to the DNA groove [6]. In a phase ½ study, a phase 1 part determined the suggested dose for phase 2(RP2D) for the safety and antitumor activity of InO distributed every week to patients with CD22-positive Relapse/Refractory B-cell ALL. Out of all the 72 patients treated, 68% achieved CR/CRi with a medium time of 27 days. 84% of them achieved measurable residual disease negativity while 37% relapsed within a month. Of the patients who received RP2D, 69% achieved CR/CRi. The recorded CR/CRi rate is 30-40% higher than the traditional chemotherapy after the first trial and 10-20% in the last trial [7].

2.2.2. CAR-T cell therapy

CD19 is a protein expressed on B cell surface during cell development, and it is displayed on ALL. Its comprehensive expression on B cell malignancies enables CD19 to be used in CAR-modified T cell therapy.

CAR-T therapy using CD19 has shown a high Complete Response rate in adults and pediatric patients with B-cell ALL caused by relapse [8]. Meanwhile, high competence has been demonstrated by CD20-targeted CAR-T cell therapy alone or in combination with CD19 in vitro and in vivo animal models of ALL. A dual-target CAR-T cell is modified using either CD20 or CD22 to increase the curing rate and decrease the rate of relapse. However, CAR-T cell therapy is not 100% efficient, patients will still experience relapse.

From the trials carried out, this bispecific CAR-T cell eliminates the combined CD19+ CD20+/CD20- phenotype in pediatric ALL transplanted. This is in comparison with anti CD22 CAR-T cells alone which have left some CD22-leukemia cells without curing ALL and there could be a higher refractory rate. Consequently, in can be found that anti-CD19-CD20 bispecific CAR-T cells are able to diminish the relapse rate caused by the loss of antigen in leukemia cells in a long term compared to single CAR-T cells [8].

Relapse occurs when a positive blast grows again and this is usually the result due to the loss of persistence in CAR-T cells; the efficiency of CAR-T cells eliminating leukemia will be decreased. Although boosting T-cell persistence has been carried out, CD-19 positive blasts still grow. A group at a national cancer institution recognized that negative blasts develop in patients who maintain CD22 expression after CD19 CAR-T treatment. Hence CD22 CAR-T cells that are used to treat CD19 negative relapse and is possible to be integrated with CD19-modified CAR are developing, hoping that CD22 CAR-T cells can prevent the relapse caused by antigen escaping [9]. CRS and neurotoxicity at low levels are observed with self-limiting ability in CD22 CAR-T therapy which is in contrast to CD19 CAR-T therapy. Although CD19 CAR-T therapy has a high complete remission (CR) rate with a percentage of 70-90 in ALL, some patients have shown no response and some even experienced relapse within one year. A current investigation carried out by Fry. et al. on patients who have failed CD19 CAR-T therapy has shown the efficacy of CD22 CAR-T therapy as it induces CRS in a considerable amount [10].

2.3. Current drawbacks and limitations

Infusion of CAR T cells is associated with toxic-related syndromes such as cytokine release syndrome (CRS). It is possibly related to a developmental inflammatory process triggered and preserved by the activation led by encounterment of infused CAR T cells and targeted CD19 antigen [11]. CRS is often referred as hyperpyrexia, hypotension, and neurotoxicity. B cell aplasia is another prevalent side effect which is served as an indirect marker to demonstrate the persistency of anti-CD19 and CD20 CAR-T cells. CAR-T cell expansion in toxicities is

complex to be clearly defined due to variation in the amount given by the dose of drug; the T cell phenotype composition extracted for genetic modification and the difference in chemotherapy regimens for different patients [8]. Even though CAR-T therapy is more precise than chemotherapy, the relapse rate is relatively high as it can not reach all the cells in the body which chemotherapy is capable of. In some circumstances, relapse is not only caused by the loss of CD protein antigen, but also can be triggered by a reported mechanism called lineage switch. The most common case is ALL switching to AML which is an immunophenotypic change, and this event usually occurs during the treatment of acute leukemia. In another study, 4 patients who have experienced relapse still had CD22 expression on the cell surface. Hence some other factors may contribute to relapse conditions as well [10]. As for chemotherapy, measurable residual disease (MRD) is detected when circulating cancer cells present and chemoresistance occurs.

In addition, pediatric fatality is usually caused by chemotherapy itself rather than leukemia. Most patients experience at least one from mucositis, infections and acute toxicities. Toxicities involving CNS toxicities occur in 10%-15% of the patients with pediatric ALL with overlapping symptoms [12]. Every organ will be affected by chemotherapy and there is a potential that normal healthy cells may undergo mutation and lead to a newly developed cancer.

Yet, compared with traditional chemotherapy, the immunotherapy involving CAR-T only targets tumor and cancerous cells with greater precision. Although chemotherapy is efficient at killing cancerous cells around the body, normal healthy cells will be affected. A mutation may be triggered, and patients will need to receive chemotherapy again. On the contrary, mbA and CAR-t cell therapy lack the ability to sieve out metastasis cancerous cells while chemotherapy does not.

3. ACUTE MYELOID LEUKEMIA (AML)

3.1. Mechanism of AML

AML begins developing in the bone marrow and often spreads into the blood, lymph nodes and CNS. This is when the bone marrow makes monocytes at a fast pace which leads to a dysfunction consisting of unexpected expansion and differentiation of myeloid stem cells. The typical maturation pathway of myeloid precursor cells will be altered, and 97% of AML cases are caused by genetic mutations [9].

3.2. Newly developed treatment for acute myeloid leukemia

3.2.1. FLT3 Inhibitors

This treatment works by inhibiting tyrosine kinase receptors and has succeeded in curing solid and hematological malignancies.

Internal tandem duplication (ITD) is perceived the most in genetic abnormality and leukocytosis during examination and the risk of relapse after traditional chemotherapy. Missense mutations of the tyrosine kinase domain (TKD) exist as well though there is a low probability of occurrence in AML. Both ITD and TKD end up in FLT3 signaling activation. Consequently, cellular proliferation, anti-apoptosis and blocked differentiation are sometimes observed in AML. FLT3 inhibitors can be categorized into the first and the second generation according to their development. Multi-kinase inhibitors are described as the first generation, for instance, sorafenib, which has demonstrated its efficiency in reducing the number of leukemic cells and achieving CR in patients. In a recent study, Rolliget et al. have carried out an investigation by applying the consolidation of sorafenib with basic chemotherapy to 267 patients aged not older than 60 with newly diagnosed AML in a phase II trial which has different treatments distributed to two groups. Two rounds of induction therapies called 7+3 were randomly distributed to patients to determine whether more treatments should be distributed or not , followed by three rounds of intense cytarabine consolidation therapy incorporated with either sorafenib or placebo distributed twice a day at a level of 400 mg. Meanwhile, a sorafenib maintenance therapy was administrated to the sorafenib group at the end of the cycle for 12 months. Overall 40% of the patients has reached event free survival in the sorafenib group compared to placebo group with a lower rate of 20% [13] [14].

The second generation of inhibitors are those which have greater precision and effectiveness against FLT3 including quizartinib and gilteritinib. CR/CRi of 23%-57% and a 9-20 weeks medium duration of response. Several phase 3 trials have indicated that quizartinib has improved the overall survival contrasting with salvage chemotherapy in Relapse/Refractory FLT3-mutated AML. FLT3-ITD AML cells express a high rate of protein synthesis to keep oncogenic proteins level within the cell. Omacetaxine mepesuccinate (OME), an effective FLT3 inhibitor assisting the initial therapy, is recognized to inhibit the elongation of protein FLT3 with an acceptable toxicity amount. This process represses FLT3 subsequent signaling [14].

3.2.2. Immunotherapy

CD33 and CD123 are the two lineage-restricted antigens in AML, with a blast expression of 90% and between 50% to 100%. The myeloid traits have CD33 presented and is used in monoclonal antibody and CAR-T cell therapy while CD123 is the IL3 receptor alpha chain, and its expression is greater in FLT3-ITD-mutated AML than in those without this mutation. Gemtuzumab ozogamicin (GO) is an anti-drug targeting CD33 and it is adjoined to calicheamicin, and there are studies showing its positive relationship with anti-leukemia effect and subsequent relapse. By combining chemotherapy with GO at a low dose, efficacy has been observed due to limited toxicity [15]. A rate of 63% in overall response in relapsed cases has been shown in CD33-positive AML, accompanied by

survival benefits in newly diagnosed cases consolidating with traditional chemotherapy [16].

The first CD33-targeted BiTE, named AMG 330 has shown prolonged survival in human AML-transplanted immunodeficient mice. CD33 is an ideal antigen for developing CAR-T therapy, and six discrete second-generation CD33 CAR-Ts are invented in an experiment to find the most effective CD33 CAR-T cell [17]. Wang et al. have carried out a clinical trial in which CD33-directed autologous CAR-T therapy was given to a patient with refractory AML, and 9 weeks of blasts present in marrow was marked [18].

CD123 expressed on leukemic stem cells is related to the possibility of treatment defeat. An investigation interpreting patient samples has demonstrated the common co-expression of CD123, CD25, and CD99 in CD34-positive leukemic cells in FLT3-ITD-mutated AML. Selective anti-tumor effects of CD123-directed CAR-T leukemia cells are demonstrated by a study using AML-transplanted mice. These mice have shown that CD123-directed CAR-T cells have specific anti-tumor effects on leukemic cells [16].

Meanwhile, T cells which can secrete bispecific CD123/CD3 antibodies have been engineered and effects of leukemia elimination have been expressed in a xenograft mouse model [16]. CD123-ENG cells are generated through transduction. To demonstrate the specifity of CD123-ENG T cells against tumor cells' expression of the antigen target, a panel consisting of both CD123 positive and negative cell lines is used. The eliminating potential of CD123 ENG cell against positive antigen is confirmed by the successful lysis of AML cells displaying CD123 antigen [19].

3.3. Current drawbacks and limitations

For FLT3-ITD inhibitors, failed treatment is related to the mutation of D835Y and D835H within the FLT3 TKD. Although longer periods of disease-free survival are achieved in early-phases trials of combination therapy, relapse follows inevitably within months after the treatment [13]. Drug resistance is related to relapse of leukemia and there could be protection towards leukemia cells by BM microenvironment and leukemia cells adaptation against FLT3 inhibitors. In some clinical studies, leukemia clones bringing FLT3-TKD mutations at relapse is an urgent situation in FLT3 inhibitors treatment [14].

Though CD33 and CD123 are studied the most among other antigens, myelosuppression has been the major concern due to its display on healthy hematopoietic tissues [15]. In addition, though GO has shown a 23-33% overall remission rate, high levels of liver and hematological toxicities are accompanied as well. Single-agent treatment may show a greater adverse event (AE) rate. In a recent monotherapy study of GO, 22% of the patients have demonstrated grade 5 adverse events caused by ALL. At the same time, 60%, 55% and 78% of patients have experienced grade 3 and 4 AEs which were linked to the treatment as well. For instance, hepatotoxicity, veno-occlusive disease, and drug-induced liver injury had occurred in five patients. On the contrary, a rate of longer survival along with an increased rate of overall remission has been achieved with the addition of cytarabine and mitoxantrone to GO monotherapy [20].

4. CONCLUSION

Both AML and ALL can be treated with immunotherapy such as CAR-T and monoclonal antibodies, and these two therapies are still developing. Yet the current technologies are unable to assess each method. As mentioned above, the difference between a single agent and multiple agents in monotherapy is indicated by varying levels of an adverse event, whereas in multiple agent treatment, the overall remission rate has significantly boosted in AML patients. In ALL where an infusion of CAR-T cells has been implemented and encountered with antigens, CRS seems to be inevitable. The significance level not only depends on the amount of dose being distributed but also the factors such as the previous treatments received by patients. Hence, it is sophisticated to make a conclusion on CRS. Furthermore, although most relapse in leukemia is thought to be caused by the loss of specific antigens, in the case of CD22, relapse still occurs when patients have CD22 expression. This contradicts to the popular claims that the immune escape of antigen is the main cause of relapse. Consequently, future research can focus on figuring out what the other important causes are. This shows the limited view and knowledge humans possess nowadays. As for CD33 mbA in AML, myelosuppression often ensues. The bone marrow activity along with the ability of red blood cell production declines as a side effect of cancer treatment of AML, resulting in short breath and fatigue. The benefits of the treatments above can be seen to outweigh the harm they bring. CAR-T and mbA are much better than conventional chemotherapy in precision as they target cancerous cells or the cells that express a specific antigen, such as CD19, CD20, CD22, CD23, and CD123.

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